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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/070,480 | 07/08/2002 | Takahisa Nakai | 12178/2 | 4713 |

26646 7590 08/04/2005

KENYON & KENYON
ONE BROADWAY
NEW YORK, NY 10004

| EXAMINER | |
|---|---|
| ODELL, LINDSAY T | |
| **ART UNIT** | **PAPER NUMBER** |
| 1656 | |

DATE MAILED: 08/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/070,480 | NAKAI ET AL. | |
| | Examiner | Art Unit | |
| | Lindsay Odell | 1656 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *20 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *2,3 and 8-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 4-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 February 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *30 April 2002*; *28 February 2002*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet*.

## DETAILED ACTION

### *Application Status*

1. The instant Application, filed on July 8, 2002, is the national stage application of international application PCT/JP00/05901, filed on August 20, 2000. In response to the previous Office action, a written restriction requirement (mailed on April 21, 2005), Applicants filed a response received on May 20, 2005. Claims 1-35 are pending in this instant Office action.

### *Election*

2. Applicant's election, with traverse, of Group II, Claims 1 and 4-7, drawn to a decarbamylase crystal having space group $P2_12_12_1$ and an amino acid sequence set forth in SEQ ID NO: 2, in the reply filed on May 20, 2005 is acknowledged. Applicant has provided no reasons for the traversal. The requirement is still deemed proper, and is, therefore, made FINAL. Claims 1-35 are pending in the instant Office action. Claims 2-3 and 8-35are withdrawn as non-elected inventions. Claims 1 and 4-7, to the extent they read on the crystal having space group $P2_12_12_1$ and SEQ ID NO: 2 are examined herein.

### *Priority*

3. The instant application is granted the benefit of priority for the foreign application 11-246797 filed in Japan on August 31, 1999, as requested in the declaration. Receipt is acknowledged of papers submitted under 35 U.S.C. § 119(a)-(d) or (f), which papers have been placed of record in the file. Said papers are not in English and no translation has been filed.

***Information Disclosure Statement***

4. The information disclosure statement filed on February 28, 2002 has been reviewed, and its references have been considered as shown by the Examiner's initials next to each citation on the attached copy.

5. The information disclosure statement (IDS) filed April 30, 2003 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. The following reference were not considered for the reasons described below:

a) The copy of the document Hilgenfeld *et al.* is incomplete.

All other documents in said Information Disclosure Statement were considered as noted by the examiner's initials in the attached copy.

***Compliance with Sequence Rules***

6. The sequence listing, filed in computer readable form (CRF) and paper copy on July 8, 2002, has been received and entered. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to **fully** comply with the requirements of 37 C.F.R. § 1.821 through 1.825; Applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990).

a) On page 25, Table 1, sequences of decarbamylase that correspond to particular secondary structure elements are disclosed without SEQ ID NO identification.

If the noted sequences are in the sequence listing as filed, Applicants must amend the specification to identify the sequences appropriately by SEQ ID NO. If the noted sequences are not in the sequence listing as filed, Applicants must provide (1) a substitute copy of the sequence listing in both computer readable form (CRF) and paper copy, (2) an amendment directing its entry into the specification, (3) a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. § 1.821 (e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d), and (4) any amendment to the specification to identify the sequences appropriately by SEQ ID NO.

***Objections to the Specification***

7. The specification is objected to because the title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: ---Crystals of *E. coli* decarbamylase---. Appropriate correction is required.

8. The abstract of the disclosure is objected for not completely describing the disclosed subject matter (MPEP § 608.01(b)). It is noted that in many databases and in foreign countries the Abstract is crucial in defining the disclosed subject matter; thus, its completeness is essential. The Examiner suggests inclusion of the source species of decarbamylase (*Escherichia coli* and *Agrobacterium* sp., as indicated in the sequence listing), and methods of making decarbamylase crystals, for completeness. Appropriate correction is required.

9. The disclosure is objected for being confusing in Table 4. Table discloses to particular amino acid residues that cause thermostability when mutated; however, without any reference to a sequence, it is unclear exactly which residues are mutated. Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1 and 5-7 are rejected under 35 U.S.C. 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The instant claims are drawn to decarbamylase crystals having space group $P2_12_12_1$ and an amino acid sequence as set forth SEQ ID NO: 2. While the structure of one species of said genera of crystallized complexes is disclosed in the specification, structural and functional limitations adequate to describe the instant genera of crystallized complexes are lacking.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed.

Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

In the instant specification, decarbamylase crystals with space group $P2_12_12_1$, unit cell parameters a = 81.5-82.5 Å, b = 133.0-135.0 Å and c =119.5-121.5 Å amino acid sequence SEQ ID NO: 2 are disclosed (see page 6). These crystals are not representative of the claimed genera of crystals because a correlation of structure and function for the claimed genera is not disclosed. For each crystal, polypeptides having specific sequences are crystallized forming a specific crystal with particular unit cell dimensions and a particular space group. The unit cell dimensions and space group are affected by other molecules (ligands, metals) present in the crystal. Thus, to adequately describe a protein crystal's structure, claims must include the following structural limitations: composition (amino acid sequence and any ligands), unit cell dimensions and space group. However, the instant claims are drawn to crystals having unspecified unit cell dimensions. For these reasons, the instant claims lack adequate written description. See also Case 4 of the Trilateral Project on protein 3D structure related claims at http://www.uspto.gov/web/tws/wm4/wm4_index.htm.

11. Claims 1 and 4-7 are rejected under 35 U.S.C. 112, first paragraph, enablement. The claim(s) contain subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The instant claims are drawn to decarbamylase crystals with space group $P2_12_12_1$ and an amino acid sequence as set forth SEQ ID NO: 2 (claims 1 and 5-7) and unit cell dimensions a = 81.5-82.5 Å, b = 133.0-135.0 Å and c =119.5-121.5 Å (claim 4). To make the crystals encompassed by the scope of the instant claims would require undue experimentation.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the

breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

The instant specification discloses a how to make decarbamylase crystals with unit cell dimensions a ≅ 66.92 Å, b≅ 135.50 Å and c≅ 67.30 Å with and without sodium ethylmercurithiosalicylate (ETMS) on pages 46-48. The space group of these crystals is not disclosed. The amino acid sequence is that of *Agrobacterium* sp. since decarbamylase was obtained (see page 46) by the method taught by Nanba *et al.*, who teach the cloning and isolation of the decarbamylase from *Agrobacterium* sp. (see page 46).

However, no working examples of how to make crystals with space group $P2_12_12_1$, amino acid sequence SEQ ID NO: 2 (*E. coli* decarbamylase) and unit cell dimensions a = 81.5-82.5 Å, b = 133.0-135.0 Å and c =119.5-121.5 Å are found. While the art and the specification provide some guidance on making decarbamylase crystals (see page 14-15 and 17), this guidance is insufficient to produce the particular crystals encompassed by the scope of the claims. In order to make protein crystals, the following must be clear: the preparation and chemical composition of the molecules to be crystallized, and the crystallization conditions, including the type and amount of methods and reagents used. Crystallization experiments must be done in order to determine if a macromolecule will crystallize, and X-ray diffraction experiments must be done in order to determine if the crystalline macromolecule is encompassed by the scope of the claims. The guidance found in the specification for crystallization conditions (i.e. range of precipitant used, i.e. types of heavy metals/heavy metal compounds) is too broad to be useful. Small changes in any of the aforementioned factors can change the unit cell dimensions and space group symmetry of a crystal dramatically (Giege, 1994, see PTO-892; McPherson, 1995, see

PTO-892); therefore, precise instruction about how to make protein crystals is required so that undue experimentation is not required. Due to the unpredictable nature of the art, specific information on how to make each crystal encompassed by the scope of the claims is required for enablement. One of skill in the art would be unable to predict how to make any members of the genus encompassed by the scope the claims; to do so would require undue experimentation. Therefore, the instant claims are not enabled.

***Other Art for Comment/Examiner's Suggestions***

The following are cited to complete the record:

a) Nakai *et al.* (see IDS) teach crystals of the *Agrobacterium* sp. decarbamylase in space group $P2_12_12$, with unit cell dimensions a = 67.84 Å, b = 137.83 Å and c = 68.4 Å, which shares 99.1% identity to *E. coli* decarbamylase (SEQ ID NO: 2), and WO 94/03613 (see IDS) teaches the amino acid sequence for *E. coli* decarbamylase (see attached alignment to SEQ ID NO: 2). However, neither document teaches crystallization of *E. coli* decarbamylase in a particular space group or unit cell dimensions, nor would it be obvious to make crystals of *E. coli* decarbamylase in a particular space group or unit cell dimensions.

***Conclusion***

12. Claims 1 and 4-7 are rejected for the reasons identified in the numbered sections of the Office action. Applicants must respond to the objections/rejections in each of the numbered sections in the Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lindsay Odell whose telephone number is 571-272-3445. The examiner can normally be reached on M-F, 8:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lindsay Odell, Ph.D.
July 13, 2005

KATHLEEN M. KERR, PH.D.
SUPERVISORY PATENT EXAMINER

Continuation of Attachment(s) 6). Other: Amino Acid Database Alignment to SEQ ID NO: 2 .

Uniprot 03 Database

Alignment to SEQ ID NO: 2

```
RESULT 1
DCAS_AGRSK
ID   DCAS_AGRSK     STANDARD;      PRT;   304 AA.
AC   P60327;
DT   29-MAR-2004 (Rel. 43, Created)
DT   29-MAR-2004 (Rel. 43, Last sequence update)
DT   25-OCT-2004 (Rel. 45, Last annotation update)
DE   N-carbamoyl-D-amino acid hydrolase (EC 3.5.1.77) (D-N-alpha-
DE   carbamilase).
OS   Agrobacterium sp. (strain KNK712).
OC   Bacteria; Proteobacteria; Alphaproteobacteria; Rhizobiales;
OC   Rhizobiaceae; Rhizobium/Agrobacterium group; Agrobacterium.
OX   NCBI_TaxID=252128;
RN   [1]
RP   SEQUENCE FROM N.A.
RX   MEDLINE=98312023; PubMed=9648217;
RA   Nanba H., Ikenaka Y., Yamada Y., Yajima K., Takano M., Takahashi S.;
RT   "Isolation of Agrobacterium sp. strain KNK712 that produces N-
RT   carbamyl-D-amino acid amidohydrolase, cloning of the gene for this
RT   enzyme, and properties of the enzyme.";
RL   Biosci. Biotechnol. Biochem. 62:875-881(1998).
RN   [2]
RP   X-RAY CRYSTALLOGRAPHY (1.7 ANGSTROMS).
RX   MEDLINE=20366582; PubMed=10903946; DOI=10.1016/S0969-2126(00)00160-X;
RA   Nakai T., Hasegawa T., Yamashita E., Yamamoto M., Kumasaka T.,
RA   Ueki T., Nanba H., Ikenaka Y., Takahashi S., Sato M., Tsukihara T.;
RT   "Crystal structure of N-carbamyl-D-amino acid amidohydrolase with a
RT   novel catalytic framework common to amidohydrolases.";
RL   Structure 8:729-737(2000).
CC   -!- FUNCTION: The enzyme catalyzes the hydrolysis of N-carbamoyl-D-
CC       amino acids to the corresponding which are useful intermediates in
CC       the preparation of beta-lactam antibiotics. Industrial production
CC       of beta-lactam antibiotics is now being developed using this
CC       enzyme.
CC   -!- CATALYTIC ACTIVITY: N-carbamoyl-D-amino acid + H(2)O = D-amino
CC       acid + NH(3) + CO(2).
CC   -!- SIMILARITY: Contains 1 CN hydrolase domain.
CC   ---------------------------------------------------------------------
CC   This SWISS-PROT entry is copyright. It is produced through a collaboration
CC   between the Swiss Institute of Bioinformatics and the EMBL outstation -
CC   the European Bioinformatics Institute. There are no restrictions on its
CC   use by non-profit institutions as long as its content is in no way
CC   modified and this statement is not removed. Usage by and for commercial
CC   entities requires a license agreement (See http://www.isb-sib.ch/announce/
CC   or send an email to license@isb-sib.ch).
CC   ---------------------------------------------------------------------
DR   EMBL; AB007368; BAD00007.1; -.
DR   PIR; JW0082; -.
DR   PDB; 1ERZ; X-ray; A/B=2-304.
DR   InterPro; IPR003010; Ntlse/CNhydtse.
DR   PROSITE; PS50263; CN_HYDROLASE; 1.
KW   3D-structure; Hydrolase.
FT   DOMAIN        5    299       CN hydrolase.
FT   ACT_SITE     47     47
FT   ACT_SITE    127    127
```

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FT   ACT_SITE    172    172
SQ   SEQUENCE   304 AA;  34285 MW;  C64290139C1C7E61 CRC64;

  Query Match             99.1%;  Score 1599;  DB 1;  Length 304;
  Best Local Similarity   99.0%;  Pred. No. 8e-134;
  Matches  300;  Conservative    1;  Mismatches    2;  Indels    0;  Gaps    0;

Qy          1 TRQMILAVGQQGPIARAETREQVVVRLLDMLTKAASRGANFIVFPELALTTFFPRWYFTD 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||:|||
Db          2 TRQMILAVGQQGPIARAETREQVVVRLLDMLTKAASRGANFIVFPELALTTFFPRWHFTD 61

Qy         61 EAELDSFYETEMPGPVVRPLFEKAAELGIGFNLGYAELVVEGGVKRRFNTSILVDKSGKI 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         62 EAELDSFYETEMPGPVVRPLFEKAAELGIGFNLGYAELVVEGGVKRRFNTSILVDKSGKI 121

Qy        121 VGKYRKIHLPGHKEYEAYRPFQHLEKRYFEPGDLGFPVYDVDAAKMGMFICNDRRWPEAW 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        122 VGKYRKIHLPGHKEYEAYRPFQHLEKRYFEPGDLGFPVYDVDAAKMGMFICNDRRWPEAW 181

Qy        181 RVMGLRGAEIICGGYNTPTHNPEVPQHDHLTSFHHLLSMQAGSYQNGAWSAAAGKAGMEE 240
              |||||||||||||||||||| |||||||||||||||||||||||||||||| ||||
Db        182 RVMGLRGAEIICGGYNTPTHNPPVPQHDHLTSFHHLLSMQAGSYQNGAWSAAAGKVGMEE 241

Qy        241 NCMLLGHSCIVAPTGEIVALTTTLEDEVITAAVDLDRCRELREHIFNFKQHRQPQHYGLI 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        242 NCMLLGHSCIVAPTGEIVALTTTLEDEVITAAVDLDRCRELREHIFNFKQHRQPQHYGLI 301

Qy        301 AEL 303
              |||
Db        302 AEL 304
```